

<b>Office Action Summary</b>	<b>Application No.</b> 10/561,831	<b>Applicant(s)</b> SAYERS ET AL.	
	<b>Examiner</b> Christina Borgeest	<b>Art Unit</b> 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 19 April 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-57 is/are pending in the application.
- 4a) Of the above claim(s) 24-47, 49, 50 and 53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-23, 48, 51, 52 and 54-57 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 December 2005 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☒ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |  |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)                                   |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. <u>6/28/2010</u> .  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application                                    |
| Paper No(s)/Mail Date <u>12/21/2005</u> .  | 6) <input checked="" type="checkbox"/> Other: <u>PTO-90C; Notice to Comply with Sequence Rules</u> . |

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election without traverse of Group I (claims 1-23, 48, 51, 52 and 54-57) in the reply filed on 19 April 2010 is acknowledged. Claims 24-47, 49, 50 and 53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 19 April 2010. Finally, the Examiner neglected to put a species election for the species recited in claim 2 in the Requirement for Restriction mailed 18 March 2010, thus Applicants' representative was called on 28 May 2010 in order to make a species election by telephone.

This application contains claims directed to the following patentably distinct species **MODIFIED CYTOKINE LIGAND**:

Please choose a modified cytokine ligand as recited in claim 2.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. Each modified cytokine ligand represents a separate contribution to the art. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1, 4-13, 48 and 51 are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record

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showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

During a telephone conversation with Shannon Lentz on 28 May 2010 a provisional election was made without traverse to prosecute the species of growth hormone. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-23, 48, 51, 52 and 54-57 are under examination insomuch as they read upon a modified ligand polypeptide, wherein said ligand is growth hormone.

### ***Foreign Priority***

Acknowledgment is made of Applicant's claim for foreign priority based on an application filed in the United Kingdom on 28 June 2003. It is noted, however, that applicant has not filed a certified copy of the 0315182.6 application as required by 35 U.S.C. 119(b).

### ***Specification***

The abstract of the disclosure is objected to because of the use of the legal term "said" in lines 2, 4 and 6, for example. Correction is required. See MPEP § 608.01(b).

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Applicant is reminded of the proper language and format for an abstract of the disclosure:

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Appropriate correction is required.

### ***Sequence Compliance***

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Specifically, claim 10 and the sequences disclosed in the specification at p. 7, line 5; p. 10, line 31; p. 11, lines 5 and 9 are not accompanied by the required reference to the relevant sequence identifiers. This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). Please see the PTO-90C and Revised Notice to Comply attached to the instant Office Action.

### ***Drawings***

The drawings are objected to because the Western blots in Figure 6 are too dark to make out any details. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as “amended.” If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

### ***Claim Objections***

Claims 2, 12, 13, 48, 51 are objected to because of the following informalities.

Claim 2 does not have a period at the end of the claim.

Claim 12 recites “a a-helical”, where presumably “an α-helical” was intended.

Claim 13 recites “wherein mid a receptor” in line 2. This phrase appears to be a typographical error. Further, line 3 of the claim recites “bind site”, where presumably “binding site” was intended.

Claim 48 recites non-elected inventions.

Claim 51 depends from claim 49, which is currently withdrawn.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23, 48, 51, 52 and 54-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites “[a] modified cytokine ligand polypeptide comprising a modified amino acid sequence, which is a modification of the native cytokine amino acid sequence of said ligand, wherein the native amino terminal and carboxyl terminal amino acid residues of the native polypeptide are linked...characterized in that said ligand is provided with alternative amino terminal and carboxyl terminal amino acid residues.” It is not clear whether “alternative” refers to the formation of new amino and carboxy termini as described in the instant specification at p. 2, line 27, or whether “alternative” refers to “modification”, which in the context of the instant specification at p. 2, lines 15-24 mean “variants” (amino acid substitutions, deletions, mutations). If “alternative”

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refers to "modification", then the claim is further unclear because it requires that the "native" amino acid sequence is modified or mutated in some way, but then also requires that the linked amino and carboxy termini remain "native" or unmodified. The phrase "native amino terminal and carboxyl terminal" in lines 3-4 of claim 1 is also unclear because it is not clear whether the term "native" limits just the amino terminal or whether it is also meant to limit carboxyl terminal. Claims 2-23, 48, 51, 52 and 54-57 are indefinite for depending directly or indirectly from an indefinite claim.

Claim 8 is indefinite because there is insufficient antecedent basis for "flexible linker" in claim 7, from which claim 8 depends. Claim 7 recites "flexible peptide linker."

Claim 9 is indefinite because there is insufficient antecedent basis for "linker" in claim 8, from which claim 9 depends. Claim 8 recites "flexible linker."

Claim 11 is indefinite because there is insufficient antecedent basis for "linker" in claim 5, from which claim 11 depends. Claim 5 recites "linking molecule."

Claims 15-23 and 54-57 recite "human growth hormone as represented by Figure 1." Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted). Reference characters corresponding to elements recited in the detailed description and the drawings may be used in conjunction with the recitation of the same element or

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group of elements in the claims. See MPEP § 608.01(m). Note that this rejection can be overcome by amending the claims to recite "human growth hormone as represented by SEQ ID NO: 9," as set forth in the amended specification.

Claims 15-23 and 54-57 are rejected as being indefinite because the claims recite, for example, "the alternative amino terminal and carboxyl terminal amino acids are derived from between amino acid 116 and amino acid 122 of GH." The phrase "derived from between..." is unclear because it cannot be determined whether it means the alternative amino and carboxyl terminal ends occur at the recited ranges or somewhere in-between the recited ranges.

***Claim Rejections - 35 USC § 112, first paragraph – Scope of Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23, 48, 51, 52 and 54-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified growth hormone, wherein the native amino terminal and the native carboxyl terminal of said growth hormone are linked directly or indirectly and wherein said modified growth hormone comprises the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 (referred to as CP\_01, CP\_02, CP\_03 and CP\_04 in the specification, respectively), does not reasonably provide enablement for the claims as broadly recited. The specification does not enable any person skilled in the art to

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which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

There is insufficient structural limitation of the modified cytokine ligands or modified growth hormones in the claims, rendering the claims overly broad. The terms "modified" and "modification" encompass any number of addition, mutations and deletions, with no upper limit. In addition, there is no recitation of the "alternative amino terminal and carboxyl terminal amino acid residues." Further, the claims require that "at least one binding domain for said ligand's cognate binding partner is disrupted.

According to the specification at p. 1, lines 22-28:

[A] single molecule of GH associates with two receptor molecules (GHR). This occurs through two unique receptor-binding sites on GH and a common binding pocket on the extracellular domain of two receptors. Site 1 on the GH molecule has a higher affinity than site 2, and receptor dimerization is thought to occur sequentially with one receptor binding to site 1 on GH followed by recruitment of a second receptor to site 2. The extracellular domain of the GHR exists as two linked domains each of approximately 100 amino acids. It is a conformational change in these two

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domains that occurs on hormone binding with the formation of the trimeric complex GHR-GH-GHR. (Citations omitted by Examiner).

Thus there are two sites that can be disrupted, and the specification suggests that mutations disrupting site 1 would result in a non-functioning GH incapable of binding properly and therefore, not useful as either an agonist or antagonist. Indeed, Applicants indicate at p. 4, lines 15-20 that the working examples are circular permutations of GH that result in the formation of new amino and carboxyl terminal termini, thus resulting in a disruption of site 2, rather than site 1, which is important for binding. Presumably this type of disruption results in a GH that permits “docking...via its high affinity site 1 domain but produces a complex which is incapable of activating GHR”; i.e., an antagonist, though the activity of the circularly permuted GH proteins is never tested.

The art teaches that mutations to site 1 that do not affect binding can nevertheless lead to a severe decrease in activity. See for instance, Rowlinson et al. (JBC, 1995; 270: 16833-16839) at p. 16836, right column, last paragraph, where they teach 4 point mutations at the site 1 region that result in a decrease in activity *in spite* of unchanged affinity for the receptor. There is no guidance in the specification as to how such non-functional proteins would be used. Further, the specification is broad and contemplates modified cytokine ligands that could potentially act as either agonists or antagonists of GHR (see for instance, p. 2, lines 15-20). Thus an extremely large number of possible protein structures are contemplated, many of which are inoperative embodiments (i.e., non-functional proteins). Case law directs that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which

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embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Ibid.*; *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

Regarding the recited “cytokine ligand” modifications, the number of modifications to the amino acid sequence generally possible in any given protein that can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. See Tokuriki and Tawfik, (Current Opinion in Structural Biology 2009, 19: 596-604), who teach that mutations are generally destabilizing. For instance, Tokuriki and Tawfik teach at p. 596, right column, last paragraph, that “as mutations accumulate, protein fitness declines exponentially...or even more than exponentially...So by the time an average protein accumulates, on average, five mutations, its fitness will decline to <20%.” Further, at p. 598, left column, last paragraph, Tokuriki and Tawfik notes that “50% of mutations are destabilizing, and >15% of mutations are highly destabilizing, and of the [only] about 5% of mutations that are stabilizing values...many of these mutations result

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in inactive protein.” The teachings in the art suggest that the skilled artisan would need to undergo undue experimentation to identify all of the active cytokine ligands contemplated in the claims.

Due to the large quantity of experimentation necessary to identify the large number of contemplated modified cytokine ligands, the lack of direction/guidance presented in the specification regarding and the absence of working examples directed to the same, the complex nature of the invention, the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite structural limitations on the “modified cytokine ligands”, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

***Claim Rejections - 35 USC § 112, first paragraph – Written Description***

Claims 1, 4-13, 48 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite “[a] modified cytokine ligand polypeptide” with no structural limitation. The specification teaches four circular permutations of growth hormone (GH) at pages 21-27 represented by SEQ ID NOs: 1, 3, 5 and 7 and denoted in the specification as CP\_01, CP\_02, CP\_03 and CP\_04. The four GH circular permutation

variants taught in the specification do not provide adequate written description for the broad genus of "modified cytokine ligand polypeptides"

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of "[a] modified cytokine ligand polypeptide." Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of SEQ ID NOs: 1, 3, 5 and 7, the skilled artisan cannot envision the detailed chemical structure of the encompassed modified polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a

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potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequences set forth in SEQ ID NOs: 1, 3, 5 and 7, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-8, 48 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Pastan et al. (WO 95/27732; published 19 October 1995) as evidenced by Kreitman et al. (Cytokine, 1995; 7: 311-318—on Applicants' 1449 form). Note MPEP

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2131.01, which addresses the use of more than one reference in making 35 U.S.C. 102

Rejections:

A 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:

- (A) Prove the primary reference contains an “enabled disclosure; ”
- (B) Explain the meaning of a term used in the primary reference; or
- (C) Show that a characteristic not disclosed in the reference is inherent.

In the instant case the supplementary reference is used to show that a characteristic not disclosed in the reference is inherent. This is explained in greater detail below.

Claims 1, 4-8, 48 and 51 are drawn to a modified cytokine ligand polypeptide wherein amino terminal and carboxyl terminal amino acid residues are linked (i.e., a circular protein), directly or indirectly, further wherein said amino terminal and carboxyl terminal amino acid residues are modified and further wherein at least one binding domain for said ligand's cognate receptor is disrupted (claim 1), wherein the amino terminal and carboxyl terminal amino acid residues are linked directly (claim 4); indirectly linked by a linking molecule (claim 5); wherein said linking molecule is a peptide linker (claim 6) or a flexible peptide linker (claim 7); further wherein said flexible linker is a polypeptide which comprises 5 to 30 amino acid residues (claim 8).

Pastan et al. teach a circularly permuted IL-4 protein, wherein the amino and carboxy ends are joined together, directly or through a linker (p. 2, lines 25-30; p. 3; p. 7, lines 23-29; p. 10, lines 28-34; claims 1-37), thus meeting the limitation of “directly” linking. Linkers are described at p. 7, lines 23-29; 12, lines 21-34 through p. 13, lines 1-10; claims 1-3, 14, 16 and 18, for example, GGGNGGG or GGNGG (claims 3, 14, 16, 18). A flexible linker is described in the instant specification at p. 7, lines 1-3 as a

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“peptide linker that contains 5 to 30 amino acids,” thus the linkers taught by Pastan et al. (GGGNNGGG or GGNGG) meet the claim limitations of claims 5-8. Pastan et al. also teach amino acid modifications beginning at p. 20 at line 27 and continuing on through p. 21, whole page, for instance:

“In a preferred embodiment, circularly permuted IL4 will have an additional methionine (Met) at the amino terminus to provide an initiation site. For cloning purposes, each IL4 mutant will contain alanine at the new C-terminus. This alanine is residue 104 for IL4(105-104) and constitutes an additional residue for IL4(38-37).” (See lines 13-17 of p. 21 of Pastan et al.).

Kreitman et al. is presented to provide evidence that the amino and carboxy termini of IL4 “are close to the binding site” of their cognate binding partner (i.e. receptor), IL4R (see p. 311, right column). Thus in mutating the amino and carboxy termini of IL4 and joining them via a linker, Pastan et al. are disrupting the binding domain of the ligand or IL4. Pastan et al. teach pharmaceutical compositions at pages 31, line 10-34 through p. 33, line 25, thus meeting the limitation of claim 48. Claim 51 of the instant application is a product by process claim that depends from claim 49. According to the MPEP 2113 [R-1]:

“[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.”

Pastan et al. teach “testing the activity” of their circularly permuted IL-4 molecules, for instance, see Example 1, pages 35-40, thus they also suggest a process of making the

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modified cytokine ligand as recited in claim 51. Thus claims 1, 4-8, 48 and 51 do not teach anything over the prior art.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

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be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-14, 48, 51 and 52 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-40 of copending Application No. 12/296,180. Although the conflicting claims are not identical, they are not patentably distinct from each other because looking to the specification for a definition of the "polypeptides" recited in the '180 application, it is clear that circularly permuted growth hormone is encompassed by the claims of the '180 application. The differences lie in the structural limitations of the '180 application, which recite more specifically the structure of the recited polypeptides. Nevertheless, the very broadly recited "modified cytokine ligands...wherein the the native amino terminal and carboxyl terminal amino acids residues...are linked" of the instant claims are anticipated by the more narrowly recited polypeptides of the '180 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Conclusion***

No claim is allowed.

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The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The following documents teach GH mutants with amino acid sequences similar to SEQ ID NOs: 1, 3 5 and 7, but none teach that the GH mutants are circularly permuted: WO2001/096565; WO2004/007687; WO2000/068385 and US patent publication US20040059093.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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